

10/693744

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
17 October 2002 (17.10.2002)

PCT

(10) International Publication Number  
**WO 02/080891 A1**(51) International Patent Classification<sup>7</sup>: **A61K 31/00**,  
39/395, A61P 29/00, 25/00

(21) International Application Number: PCT/SE02/00671

(22) International Filing Date: 5 April 2002 (05.04.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0101256-6 6 April 2001 (06.04.2001) SE(71) Applicant (for all designated States except US): A+ SCI-  
ENCE INVEST AB [SE/SE]; Box 3096, S-400 10 Göte-  
borg (SE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): OLMARKER, Kjell  
[SE/SE]; Gustavsgatan 35, S-431 66 Mölndal (SE). RY-  
DEVIK, Björn [SE/SE]; Laboratorietrappan 6, S-412 68  
Göteborg (SE).(74) Agent: AWAPATENT AB; Box 11394, S-404 28 Göte-  
borg (SE).(81) Designated States (national): AE, AG, AL, AM, AT, AT  
(utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA,CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE  
(utility model), DK, DK (utility model), DM, DZ, EC, EE,  
EE (utility model), ES, FI, FI (utility model), GB, GD, GE,  
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,  
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,  
MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU,  
SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TN,  
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,  
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent  
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,  
NE, SN, TD, TG).

## Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

## Published:

- with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF A TNF INHIBITOR FOR THE TREATMENT OF LOW BACK PAIN

(57) Abstract: The use of a TNF inhibitor for the production of a pharmaceutical composition for treatment of low back pain and in particular of low back pain due to local irritation of annulus related nerve fibers by disc derived substances. Also a method for treatment of low back pain is disclosed.

WO 02/080891 A1

## Use of a TNF inhibitor for the treatment of low back pain

### Field of the invention

The present invention relates to substances, pharmaceutical compositions and methods for treatment of low back pain.

### Background of the invention

5 Low back pain affects approximately 80% of the population during their lifetime in most countries. Except for being extremely common, it is also one of the most costly disorders for the society. In Sweden alone, low back pain was estimated to cost 320.000.000 U.S. dollars in 1997 (Nachemson and Jons-  
10 son 2000). The major part of the cost relates to indirect costs such as sick-compensation and reduced productivity, and only a minor part is related to direct costs such as medical care and pharmacological substances.

In a minority of the cases (5%), there may be a known cause for the pain such as intra spinal tumors, rheumatic diseases, infections and more. In these  
15 cases the treatment may be specifically aimed at the cause. However, in the majority of the cases of low back pain, the cause remains unknown. At present there is no direct way to treat low back pain with an unknown cause and existing treatment modalities only aim at symptomatic relief.

### *20 Low back pain and sciatica*

First it is necessary to make a distinction between low back pain and one specific condition that is often linked to low back pain called "sciatica". Sciatica refers to radiating pain into the leg according to the dermatomal innervation area of a specific spinal nerve root. The pain in sciatica is distinctly different from that of low back pain. In sciatica, the pain is sharp and intense, often described as "toothache-like", and radiates down into the lower extremities,  
25 below the level of the knee. The experience of the pain is closely related to the dermatomal innervation of one or more lumbar spinal nerve roots. Sciatica is also frequently related to neurological dysfunction in that specific nerve and  
30 may be seen as sensory dysfunction, reduced reflexes and reduced muscular strength. The sciatic pain thus seem to be a neuropathic pain, i.e. pain due to nerve injury, induced by sensitized axons in a spinal nerve root at the lumbar

spinal level. The pain experienced by the patient at low back pain is more dull and is diffusely located in the lower back. There is never any radiating pain into the leg.

Sciatica is the result of nerve injury, and the cause of sciatica has an anatomical correlate. Since 1934 sciatica is intimately linked to the presence of a herniated intervertebral disc (Mixer and Barr 1934). However, although most patients with sciatica will display a herniated disc at radiological examination, it is surprising that approximately 30% of an adult population at the age of 40-50 years of age with no present or previous sciatica also have disc herniations when assessed by magnetic resonance tomography, so called "silent" disc herniations (Wiesel, Tsourmas et al. 1984; Boden, Davis et al. 1990; Boos, Rieder et al. 1995; Boos, Dreier et al. 1997). The presence of silent disc herniations is intriguing to the spine research community and seems to contradict the relationship between disc herniations and sciatica.

15

#### *Scientific knowledge of the pathophysiologic mechanisms behind low back pain*

It is well known that the outer part of the annulus fibrosus of the intervertebral disc and the posterior longitudinal ligament are innervated by C-fibers (Bogduk, Tynan et al. 1981; Bogduk 1983; Kojima, Maeda et al. 1990; McCarthy, Carruthers et al. 1991; Ashton, Roberts et al. 1994; Cavanaugh, Kallakuri et al. 1995; Palmgren, Gronblad et al. 1999). Although there are no nerve fibers in the deeper part of the annulus fibrosus or the nucleus pulposus in normal discs, nerves may reach these parts in degenerated discs through annular tears (Carreon, Ito et al. 1997; Coppes, Marani et al. 1997; Freemont, Peacock et al. 1997).

25

#### *Silent disc herniations*

As presented earlier, it is known that approximately 1/3 of a normal adult population who never suffered from sciatica have radiological visible disc herniations. Since the presence of a disc herniation is so intimately linked to the symptom of sciatica this is surprising, and at present there is no valid explanation for this phenomenon. However, "silent" in this regard only implies that the disc herniations did not produce sciatica. One may assume though that they produce other symptoms.

35

Summary of the invention

It is now well known that sciatic pain does not develop unless there is both presence of disc-derived cytokines that sensitizes the axons in the nerve root to produce pain when mechanically deformed, and a mechanical component (Olmarker, Iwabuchi et al. 1998; Olmarker and Myers 1998). The herniated nucleus pulposus must be assumed to be semi-liquid and gelatinous at the time of herniation. This would be a prerequisite for the nucleus pulposus to leak out, or to herniate, from the connective tissue capsule (annulus fibrosus) that separates it from the spinal canal under normal circumstances. The fibrotic, hard nodule, i.e. the disc herniation, that may be seen by radiology and that is excised at surgery, is not the same tissue as the freshly herniated nucleus pulposus. It must therefore be considered unlikely that the gelatinous tissue herniating from the disc space would exert any mechanical deformation on the nerve root at the time of herniation. Therefore, we would not have the mechanical component that is essential for inducing the sciatic pain. One may instead assume that the semi-liquid nucleus pulposus after herniation is just "smearing" the inside of the spinal canal rather than compressing a nerve root. At this time point, radiological investigation will not reveal any disc herniation. After some time the herniation may heal, and the result will be a scar tissue formation that protrudes slightly from the annulus fibrosus into the spinal canal. This protrusion is now organized and comprises connective tissue and may be visualized by radiology and will thereby bear the characteristics of what is generally considered to be a disc herniation. This scenario has also been seen in rats undergoing experimental disc herniation. At the time of incision of the annulus fibrosus one may, after injection of air and slight manipulation of the spinal column, induce a leakage of nucleus pulposus, i.e. a disc herniation. The nucleus pulposus is gel-like and could easily be "smeared" onto the adjacent neural structures. When reoperating such rats after 4 weeks for harvest of nerve specimens, one may see a distinct nodule at the place of the incision. This nodule is hard and closely mimics the disc herniations that may be seen by radiology and that are excised at surgery in human cases.

Considering that there are nerves and nerve-receptors at the surface of the annulus one may assume that a leakage of nucleus pulposus, which comprises a number of substances known to induce nerve irritation, will in fact induce irritation of these local nerves and thus induce low back pain. Although not producing sciatica, thus rendering it to be "silent" in this regard, the nu-

cleus pulposus leakage induces low back pain according to the suggested pathophysiological mechanism.

*Low back pain in relation to sciatica.*

5 It is known that sciatica is often preceded by a few days of low back pain. Sciatica is the result of a combination of sensitization of the nerve root by herniated nucleus pulposus and mechanical deformation (Olmarker, Iwabuchi et al. 1998; Olmarker and Myers 1998). One may therefore assume that at disc  
10 herniation, the herniated nucleus pulposus will first reach the outer annulus and produce low back pain due to stimulation of the local nerves and nerve receptors and later induce sciatica when it may reach the nerve root. If we consider that all cases of sciatica and all cases of silent disc herniations have experienced low back pain at some point there will be a considerable number of cases. The life time prevalence of sciatica is 25%, and if 1/3 of all persons not  
15 having sciatica display "silent" disc herniations they will comprise 1/3 of 75% which would be 25%. Together the lifetime prevalence of low back pain due to herniation of disc material should be 50% in an adult population. This relates well to the lifetime prevalence of low back pain that is 60-80%. The remaining 10-30% may be due to other causes such as tumor and infection.

20

*Mechanism inducing the leakage of nucleus pulposus out into the spinal canal from the disc space*

There may be various causes that may initiate a leakage of disc material out into the spinal canal. The most important prerequisite would be various  
25 degrees of disc degeneration. It is known that disc degeneration starts as early as 20 years of age and induce biochemical changes of the nucleus pulposus and a disintegration of the annulus fibrosus. It is also known that there are annular tears in the annulus fibrosus that may result in leakage of nucleus pulposus material out into the spinal canal (Hilton, Ball et al. 1980; Osti, Vernon-Roberts et  
30 al. 1992). Such leakage of nucleus pulposus material only results in a minor volume and is not equivalent to a disc herniation. There would thus not be any sciatic pain but low back pain might occur as the result of stimulation of the intra spinal nerve-receptors.

Another major cause of disc injury leading to leakage of disc-derived  
35 substances is spine trauma. Spinal injury may be acquired by axial loads, side bending, flexion-extension, axial compression or extension, torsion or as the

combination of one or more of these motions. One particularly interesting cause is the "whiplash" injury that due to a quick whiplash movement induces high stresses on the intervertebral discs with obvious risks for disc injury. All these changes may result in leakage of disc material that may be the direct cause of both acute and chronic low back pain.

*Primary and secondary changes in low back pain*

In low back pain patients it is very common to see muscular pain and tenderness. Muscular injury is probably not the primary cause of back pain but rather a secondary phenomenon to disc injury. It is well known that activation of visceral afferents may induce a secondary contraction of the skeletal muscles located superficial to the site of injury. It is therefore reasonable to think that activation of nerve receptors within the spinal canal may induce a reflexory contraction of the local muscles in the lumbar spine. The proper management of the muscle pain in such case would be to block the irritation of the nerve receptor and not by symptomatic treatment of the muscle or with stabilization or inactivation achieved by orthoses.

The inventors of the present invention have thus found that one common cause for low back pain of unknown origin is due to or related to local stimulation and/or irritation of nerve fibers and receptors located in the spine and within the spinal canal, rather than to nerve injury per se. The inventors have found that this stimulation and/or irritation is due to leakage of disc-derived substances, or nucleus pulposus material, from the intervertebral disc out into the epidural space of the spinal canal. These disc-derived substances will sensitize and irritate the local nerves and nerve-receptors within the spinal canal, primarily at the surface of the annulus fibrosus and the posterior longitudinal ligament, and thereby produce low back pain. The leakage would be the result of either degenerative changes of the intervertebral disc or the result of disease or trauma.

The inventors have found that it is possible to treat low back pain by pharmacological inhibition of the disc related substance TNF that may irritate local nerve fibers at the outer annulus fibrosus and other related structures such as the posterior longitudinal ligament.

Low back pain suitable for treatment according to the invention may be the result of unknown causes (idiopathic) or be related to various kinds of spine trauma, including whiplash injury. The treatment is also efficient in cases

of low back pain where secondary changes are predominant, such as muscular tenderness.

The invention thus relates to the use of a TNF inhibitor for the production of a pharmaceutical composition for treatment of low back pain and in particular of low back pain due to local irritation of annulus related nerve fibers by disc derived substances.

The invention also relates to a method for treatment of low back pain and in particular of low back pain due to local irritation of annulus related nerve fibers by disc derived substances, wherein a TNF blocking agent or a TNF antagonist that is capable of reducing the effective amount of endogenous biologically active TNF, e.g. by reducing the amount of TNF produced, or by preventing the binding of TNF to its cell surface receptor, TNRF, is administered to a patient.

The characterizing features of the invention will be evident from the following description and the appended claims.

#### Detailed description of the invention

For the purpose of this disclosure, TNF, tumor necrosis factor, denotes what earlier was known as TNF- $\alpha$ .

Also for the purpose of this disclosure, the terms "TNF blocking agent", "TNF blocking substance", "TNF inhibitor" and "TNF antagonist" are used interchangeably.

The term "patient", as it is used herein, relates to any human or non-human mammal in need of treatment according to the invention, i.e. a human or non-human mammal suffering from low back pain.

The "low back pain", or LBP, treatable according to the present invention is pain localized in the lumbar region, without radiation below the knees and without signs of neurological dysfunction.

The term "treatment" used herein relates to both treatment in order to cure or alleviate a disease or a condition, and to treatment in order to prevent the development of a disease or a condition. The treatment may either be performed in an acute or in a chronic way.

There are several different types of TNF blocking substances and pharmacological preparations that may be used according to the invention:

- Specific TNF blocking substances, such as

- Monoclonal antibodies, e.g. infliximab, CDP-571 (Humicade™), D2E7, and CDP-870;
- Soluble cytokine receptors, e.g. etanercept, lenercept, pegylated TNF-receptor type I, TBP-1
- 5 - TNF-receptor antagonists
- Antisense oligonucleotides; e.g. ISIS-104838;
- Non-specific TNF blocking substances, such as:
  - MMP inhibitors (i.e. matrix metalloproteinase inhibitors, or TACE-inhibitors, i.e. TNF Alpha Converting Enzyme-inhibitors)
  - 10 · Tetracyclines, for example Doxycycline, Lymecycline, Oxitetracycline, Tetracycline, Minocycline and synthetic tetracycline derivatives, such as CMT, i.e. Chemically Modified Tetracyclines;
  - Prinomastat (AG3340)
  - Batimastat
  - 15 · Marimastat
  - BB-3644
  - KB-R7785
  - TIMP-1, TIMP-2, adTIMP-1 (adenoviral delivery of TIMP-1), adTIMP-2 (adenoviral delivery of TIMP-2)
  - 20 - Quinolones, for example Norfloxacin, Levofloxacin, Enoxacin, Sparfloxacin, Temafloxacin, Moxifloxacin, Gatifloxacin, Gemifloxacin, Grepafloxacin, Trovafloxacin, Ofloxacin, Ciprofloxacin, Pefloxacin, Lomefloxacin and Temafloxacin;
  - Thalidomide derivates, e.g. SelCID, i.e. Selective Cytokine inhibitors, such as thalidomide derivative, for example CC-1088, CDC-501, CDC-801, and Linomide (Roquininex®);
  - 25 - Lazaroids; nonglucocorticoid 21-aminosteroids such as U-74389G (16-desmethyl tirilazad) and U-74500
  - Prostaglandins; Iloprost (prostacyclin)
  - 30 - Cyclosporin
  - Pentoxifyllin derivatives
  - Hydroxamic acid derivatives
  - Naphthopyrans
  - Phosphodiesterase I, II, III, IV, and V-inhibitors; CC-1088, Ro 20-1724, rolipram, amrinone, pimobendan, vesnarinone, SB 207499 (Ariflo®)
  - 35 - Melancortin agonists; HP-228



## ▪ Others, such as:

- Lactoferrin, and peptides derived from lactoferrin such as those disclosed in WO 00/01730
- CT3
- 5 - ITF-2357
- PD-168787
- CLX-1100
- M-PGA
- NCS-700
- 10 - PMS-601
- RDP-58
- TNF-484A
- PCM-4
- CBP-1011
- 15 - SR-31747
- AGT-1
- Solimastat
- CH-3697
- NR58-3.14.3
- 20 - RIP-3
- Sch-23863
- Yisum project no. 11649
- Pharma projects no. 6181, 6019 and 4657
- SH-636

25

The substance or pharmaceutical composition according to the invention is administered once or repeatedly until a sustained improvement of the patient's condition is observed. The substance or pharmaceutical composition according to the invention is administered in a therapeutically effective  
30 amount, i.e. an amount that will lead to the desired therapeutical effect and thus lead to an improvement of the patient's condition.

The pharmaceutical composition according to the invention may also comprise other substances, such as an inert vehicle, or pharmaceutical acceptable adjuvants, carriers, preservatives etc., which are well known to persons  
35 skilled in the art.

According to one preferred embodiment of the invention, the pharmaceutical composition is formulated as a sustained-release preparation. The substance according to the invention may then, for example, be encapsulated in a slowly-dissolving biocompatible polymer.

- 5        The substances or pharmaceutical compositions according to the invention may be administered in any efficacious way normally used to administer TNF inhibitors. The substances or pharmaceutical compositions according to the invention may for example be injected via intra-articular, intravenous (i.v.), intramuscular (i.m.), intraperitoneal (i.p.), intrathecal (i.t.), epidural, intracerebroventricular (i.c.v.) or subcutaneous (s.c.) routes by bolus injections or by  
10       continuous infusion. They may also be administered orally (per os), e.g. in the form of oral preparations, such as pills, syrups, or lozenges. Furthermore, they may be administered by inhalation. They may also be administered intranasally. Moreover, they may be administered transepidermally, e.g. in the form of  
15       topical preparations such as lotions, gels, sprays, ointments or patches. Finally, they may also be administered by genetical engineering.

Examples of suitable doses for different administration routes are given below.

20	Per os	10-300 mg	
	i.m.	25-100 mg	
	i.v.	2.5-25 mg	
	i.t.	0.1-25 mg	daily - every 3 <sup>rd</sup> month
	inhalation	0.2-40 mg	
25	transepidermally	10-100 mg	
	intranasally	0.1-10 mg	
	s.c.	5-10 mg	
	i.c.v.	0.1-25 mg	daily - every 3 <sup>rd</sup> month
	epidurally	1-100 mg	

30

Examples of suitable doses for different TNF inhibitors are given below.

35	Preferred dosage	More preferred dosage	Most preferred dosage
----	---------------------	-----------------------------	-----------------------------

10

Lenercept

i.v.	5-200	10-100	30-80
------	-------	--------	-------

*(all doses given in mg for administration  
once every 4<sup>th</sup> week)*

5 TBP-1

i.v.	5-200	10-100	30-80
------	-------	--------	-------

*(all doses given in mg for administration  
once every 4<sup>th</sup> week)*

CDP-57110 Humicade®

i.v.	1-100	5-10	5-10
------	-------	------	------

*(all doses given in mg/kg body weight for administration as a  
single dose)*

D2E7

15 i.v.	0.1-50	0.5-10	1-10
s.c.	0.1-50	0.5-10	1-10

*(all doses given in mg/kg body weight for administration as a  
single dose)*

Iloprost

20 i.v.	0.1-2000	1-1500	100-1000
---------	----------	--------	----------

*(all doses given in µg/kg body weight/day)*

intranasally	50-250	100-150	100-150
--------------	--------	---------	---------

*(all doses given in µg/day)*

CC-1088

25 Per os	50-1200	200-800	400-600
-----------	---------	---------	---------

*(all doses given in mg/day)*

CDP-870

i.v.	1-50	2-10	3-8
------	------	------	-----

*(all doses given in mg/kg body weight for administration once  
every 4<sup>th</sup> week)*

30

s.c.	50-600	100-400	100-200
------	--------	---------	---------

*(all doses given in mg/day)*

Linomide

(Roquinimex®)

35 Per os	0.1-25	5-20	10-15
-----------	--------	------	-------

*(all doses given in mg/kg body weight/day)*

11

HP-228

i.v. 5-100 10-50 20-40  
*(all doses given in µg/kg body weight)*

ISIS-104838

5 Per os 1-100 10-50 20-50  
 S.c. 1-100 10-50 20-50  
 i.v. 1-100 10-50 20-50  
*(all doses given in mg)*

Ariflo®

10 SB 207499  
 Per os 10-100 30-60 30-45  
*(all doses given in mg/day)*

KB-R7785

s.c. 100-500 100-300 150-250  
 15 *(all doses given in mg/kg body weight/day)*

Prinomastat  
 (AG3340)

Per os 1-250 5-100 10-50  
 20 *(all doses given in mg for administration twice daily)*

Batimastat

Per os 1-250 5-100 10-50  
*(all doses given in mg for administration twice daily)*

25 Marimastat

Per os 1-250 5-100 10-50  
*(all doses given in mg for administration twice daily)*

CDC-501

30 Per os 50-1200 200-800 400-600  
*(all doses given in mg/day)*

CDC-801

Per os 50-1200 200-800 400-600  
*(all doses given in mg/day)*

It is possible to use either one or two or more substances according to the invention in the treatment of LBP. When two or more substances are used they may be administered either simultaneously or separately.

5 The substances according to the invention may also be administered in combination with other drugs or compounds, provided that these other drugs or compounds do not eliminate the effects desired according to the present invention, i.e. the effect on TNF.

10 It is understood that the response by individual patients to the substances according to the invention or combination therapies, may vary, and the most efficacious combination of drugs for each patient will be determined by the physician in charge.

The invention also provides a diagnostic preparation and a method for diagnosis. According to this method the diagnostic preparation or a substance according to the invention is administered to a patient suspected of suffering  
15 from low back pain. An improvement of the patient's condition is an indication of that the patient has low back pain.

The invention is further illustrated in the experiments and the example below, which are only intended to illustrate the invention and should in no way be considered to limit the scope of the invention.

20

### Experiments

#### I - Formation of a disc hernia in the rat following disc incision

A total of 15 Sprague Dawley rats were anaesthetized and a facetectomy of the left L4-5 facet-joint was performed. Through this exposure the L4-5 intervertebral disc was incised using a 0.4 mm diameter injection needle. The  
25 wound was closed and the rats were killed after 1 week (n=5), 2 weeks (n=5), and 4 weeks (n=5) for analysis. The analyses comprised a macro-anatomic assessment regarding degree of fibrosis at the operation site, inflammation at the site of operations, healing of the disc incision, height of the scar formed at the surface of the disc incision (disc herniation tissue) from the disc surface, and  
30 consistency of this tissue. In selected cases the disc hernia was processed for light microscopic analysis.

Just after the incision there was of course no fibrosis, inflammation or healing of the incision. Neither was there any scar formation formed at the  
35 place of incision. In some cases the incision resulted in a slight leakage of the nucleus pulposus out into the spinal canal.

One week after the incision, there was no fibrosis and only one case with inflammatory reaction. Two of five discs were considered to be healed after the incision. Three of five discs displayed disc scars that resembled disc herniations.

- 5        Two weeks after the incision, fibrosis was more pronounced than after one week whereas inflammatory changes were similar. Healing of the disc was present in all five animals. Similar to the discs observed after one week, these discs showed scar tissue formation in three out of five discs.

- 10       Four weeks after incision, slight fibrosis was seen in all animals but no inflammation. Four of the five discs showed healing and slight to pronounced formation of scar tissue resembling disc herniations. One disc was still open and had no scar formation.

- 15       Microscopic evaluation showed that the scar tissue comprised collagen and various cell-types. These were mainly fibroblasts but there were also inflammatory cells and chondrocyte-like cells, presumably disc cells.

The results are illustrated in Table I below.

14

Table I - Disc incision in the rat

	F	I	H	Disc h.	Disc c.
1 week:					
	0	0	0	0	0
	0	0	+	(+)	+
	0	0	+	0	0
	0	0	0	++	(+)
	0	+	0	++	(+)
2 weeks:					
	(+)	0	+	(+)	(+)
	+	+	+	++	(+)
	0	0	+	0	0
	0	0	(+)	(+)	(+)
	(+)	0	+	0	0
4 weeks:					
	(+)	0	+	++	(+)
	(+)	0	0	0	0
	(+)	0	+	++	+
	(+)	0	+	+	(+)
	(+)	0	+	(+)	+

F = fibrosis, I = inflammation, H = healing of disk incision,

Disc h = height of formed disc hernia, Disc c = consistency of formed disc hernia.

5

F, I, H, Disc h

0 = no changes

(+) = slight changes

+ = clear changes

++ = pronounced changes

Disc c

0 = nothing

(+) = soft

+ = hard and elastic

++ = hard like bone

10

II - Fate of acutely injected nucleus pulposus into the epidural space of pigs

Nucleus pulposus from intervertebral discs from pigs used for other purposes were harvested. The nucleus pulposus was mixed with barium sulphate powder (Mixobar® High Density, Astra Tech, Mölndal, Sweden) and a soluble iodine-contrast medium (Urografin®, Schering AG, Berlin, Germany). Approximately 0.5 teaspoon of Mixobar powder and 0.2 ml of Urografin was added to the content of two intervertebral discs. Great care was taken to preserve the physical properties of the nucleus pulposus.

In a total of three dead pigs used for other purposes the 3<sup>rd</sup> lumbar vertebra was exposed through an abdominal approach. An injection needle (approximately 1 mm in diameter) connected to a syringe with the prepared nucleus pulposus was entered through the disc to the spinal canal under fluoroscopic guidance. The tip of the injection needle was placed in the spinal canal just outside the disc at the dorsolateral portion of the disc, i.e. where most disc

herniations occur. The volume of 1 – 1.5 intervertebral discs of prepared nucleus pulposus was slowly injected into the spinal canal, thus performing an experimental acute disc herniation. The distribution of the radiopaque nucleus pulposus was studied using a digital X-ray equipment and images were collected.

Contrary to what could be expected from the common understanding, the nucleus pulposus did not form a bulge or nodule that compressed the nerve tissue of the spinal canal. Instead, the nucleus pulposus was evenly spread in the spinal canal and did not compress either the nerve root or the thecal sac.

### III - Disc incision on the antero-ventral aspect of lumbar intervertebral discs in the pig

One pig was anaesthetized by an intramuscular injection of 20 mg/kg body weight of Ketalar (ketamine 50mg/ml; Parke-Davis, Morris Plains, New Jersey), an intravenous injection of 20 mg/kg body weight of Hypnodil (methomidate chloride 50 mg/ml; AB Leo, Helsingborg, Sweden), and 0.1 mg/kg body weight of Stresnil (azaperon 2 mg/ml; Janssen Pharmaceutica, Beerse, Belgium). Anesthesia was maintained by additional intravenous injections of 2 mg/kg body weight of Hypnodil and 0.05 mg/kg body weight of Stresnil.

Using a retroperitoneal approach, the antero-ventral aspect of the disc between the 4<sup>th</sup> and 5<sup>th</sup> lumbar vertebrae was exposed. The annulus fibrosus was incised using a scalpel. The wound was closed and one week later the pig was reanaesthetized and killed by an overdose of potassium chloride. The 4<sup>th</sup> and 5<sup>th</sup> lumbar vertebrae including the incised disc were removed *en bloc*.

Macroscopic examination revealed that the disc had healed with a fibrotic scar. The scar was dense and mainly comprised collagen and various cell-types at microscopic examination. The cells were mainly fibroblasts, but there were also inflammatory cells and cartilage-like cells in the newly formed scar.

### Summary of the data of the three experiments

It is generally assumed that when an intervertebral disc herniates, the viscous center of the disc (nucleus pulposus) is pressed out of the disc through an opening in the annulus fibrosus and forms a hard nodule at the surface of the disc that compresses the adjacent nerve root. This is thought to be the



mechanism inducing nerve root pain (i.e. sciatica). However, it is not understood why disc herniations may be accidentally seen in almost a third of all persons undergoing radiological examination that has never had sciatica. Such asymptomatic disc herniations are called "silent disc herniations". The data  
5 from the three experimental studies clearly demonstrate that contrary to what is believed, acutely herniated nucleus pulposus does not compress intra spinal nervous tissues since it is semi-fluid in consistency at the time of herniation. Instead, the hard nodule that may compress a nerve root is a scar that is formed at the surface of the disc as the result of nucleus pulposus leakage. Since nerve  
10 root pain may only occur due to the combined action of sensitization of the nerve by nucleus pulposus derived cytokines and simultaneous mechanical deformation of the nerve tissue, nerve root pain will not occur since the acutely herniated nucleus pulposus will not mechanically affect the nerve root. When a scar is formed at the disc surface, which may induce mechanical deformation  
15 of the adjacent nerve root, the cytokine-activity is no longer present in the herniated nucleus pulposus. In this situation we thus have a "silent disc herniation" that may be observed by radiological examination. However, the next time there will be leakage of nucleus pulposus from the same or adjacent discs, we have a situation of both sensitization and mechanical deformation, which  
20 will result in nerve root pain.

#### Example

A 42-year old man was given infliximab, a selective monoclonal antibody that inhibits only TNF, at 5 mg/kg for treatment of Low Back Pain. The  
25 symptoms of his LBP were primarily pain in the lumbar region and muscular tenderness.

Approximately one and a half hours after completing the administration of the test substance he started to feel symptom relief regarding his LBP. The improvement was found to be dramatic at the follow-up examinations and per-  
30 sisted during the whole study period (4 weeks).

## REFERENCES

- Ashton, I. K., S. Roberts, et al. (1994). "Neuropeptides in the human intervertebral disc." J Orthop Res 12(2): 186-92.
- 5 Boden, S. D., D. O. Davis, et al. (1990). "Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation." J Bone Joint Surg [Am] 72(3): 403-8.
- Bogduk, N. (1983). "The innervation of the lumbar spine." Spine 8(3): 286-93.
- Bogduk, N., W. Tynan, et al. (1981). "The nerve supply to the human lumbar  
10 intervertebral discs." J Anat 132(Pt 1): 39-56.
- Boos, N., D. Dreier, et al. (1997). "Tissue characterization of symptomatic and asymptomatic disc herniations by quantitative magnetic resonance imaging." J Orthop Res 15(1): 141-9.
- Boos, N., R. Rieder, et al. (1995). "1995 Volvo Award in clinical sciences. The  
15 diagnostic accuracy of magnetic resonance imaging, work perception, and psychosocial factors in identifying symptomatic disc herniations." Spine 20(24): 2613-25.
- Carreon, L. Y., T. Ito, et al. (1997). "Neovascularization induced by anulus and its inhibition by cartilage endplate. Its role in disc absorption." Spine 22(13):  
20 1429-34; discussion 1446-7.
- Cavanaugh, J. M., S. Kallakuri, et al. (1995). "Innervation of the rabbit lumbar intervertebral disc and posterior longitudinal ligament." Spine 20(19): 2080-5.
- Coppes, M. H., E. Marani, et al. (1997). "Innervation of "painful" lumbar discs." Spine 22(20): 2342-9; discussion 2349-50.
- 25 Diamant, B., J. Karlsson, et al. (1968). "Correlation between lactate levels and pH in discs of patients with lumbar rhizopathies." Experientia 24: 1195-6.
- Freemont, A. J., T. E. Peacock, et al. (1997). "Nerve ingrowth into diseased intervertebral disc in chronic back pain." Lancet 350(9072): 178-81.
- Goupille, P., M. I. Jayson, et al. (1998). "The role of inflammation in disk herniation-associated radiculopathy." Semin Arthritis Rheum 28(1): 60-71.
- 30 Hashizume, H., M. Kawakami, et al. (1997). "Histochemical demonstration of nitric oxide in herniated lumbar discs. A clinical and animal model study." Spine 22(10): 1080-4.
- Hilton, R. C., J. Ball, et al. (1980). "Annular tears in the dorsolumbar spine."  
35 Ann Rheum Dis 39(6): 533-8.

- Kang, J. D., H. I. Georgescu, et al. (1996). "Herniated lumbar intervertebral discs spontaneously produce matrix metalloproteinases, nitric oxide, interleukin-6, and prostaglandin E2." Spine 21(3): 271-7.
- Kang, J. D., H. I. Georgescu, et al. (1995). "Herniated cervical intervertebral discs spontaneously produce matrix metalloproteinases, nitric oxide, interleukin-6, and prostaglandin E2." Spine 20(22): 2373-8.
- Kojima, Y., T. Maeda, et al. (1990). "Nerve supply to the posterior longitudinal ligament and the intervertebral disc of the rat vertebral column as studied by acetylcholinesterase histochemistry. I. Distribution in the lumbar region." J Anat 169: 237-46.
- Marshall, L. L., E. R. Trethewie, et al. (1977). "Chemical radiculitis. A clinical, physiological and immunological study." Clin Orthop(129): 61-7.
- McCarthy, P. W., B. Carruthers, et al. (1991). "Immunohistochemical demonstration of sensory nerve fibers and endings in lumbar intervertebral discs of the rat." Spine 16(6): 653-5.
- Mixter, W. J. and J. S. Barr (1934). "Rupture of the intervertebral disc with involvement of the spinal canal." N Engl J Med 211: 210-215.
- Nachemson, A. and E. Jonsson (2000). Neck and back pain, Lippincott, Williams & Wilkins.
- Olmarker, K., M. Iwabuchi, et al. (1998). "Walking analysis of rats subjected to experimental disc herniation." Eur Spine J 7(5): 394-9.
- Olmarker, K. and K. Larsson (1998). "Tumor necrosis factor alpha and nucleus-pulposus-induced nerve root injury." Spine 23(23): 2538-44.
- Olmarker, K. and R. R. Myers (1998). "Pathogenesis of sciatic pain: role of herniated nucleus pulposus and deformation of spinal nerve root and dorsal root ganglion." Pain 78(2): 99-105.
- Osti, O. L., B. Vernon-Roberts, et al. (1992). "Annular tears and disc degeneration in the lumbar spine. A post-mortem study of 135 discs." J Bone Joint Surg Br 74(5): 678-82.
- Palmgren, T., M. Gronblad, et al. (1999). "An immunohistochemical study of nerve structures in the annulus fibrosus of human normal lumbar intervertebral discs." Spine 24(20): 2075-9.
- Wiesel, S. W., N. Tsourmas, et al. (1984). "A study of computer-assisted tomography: I. The incidence of positive CAT scans in an asymptomatic group of patients." Spine 9: 549-551.

## CLAIMS

1. Use of a TNF inhibitor for the production of a pharmaceutical composition for treatment of low back pain.
- 5 2. Use of a TNF inhibitor for the production of a diagnostic preparation for diagnosis of low back pain.
3. Use according to claim 1 or 2, wherein said low back pain is due to local irritation of annulus related nerve fibers by disc derived substances.
4. Use according to claim any one of the claims 1-3, wherein said  
10 TNF inhibitor is a specific TNF blocking substance.
5. Use according to claim 4, wherein said specific TNF blocking substance is an antibody.
6. Use according to claim 5, wherein said specific TNF blocking substance is a monoclonal antibody.
- 15 7. Use according to claim 6, wherein said monoclonal antibody is infliximab.
8. Use according to claim 6, wherein said monoclonal antibody is CDP-571.
9. Use according to claim 6, wherein said monoclonal antibody is  
20 CDP-870.
10. Use according to claim 6, wherein said monoclonal antibody is D2E7.
11. Use according to claim 4, wherein said specific TNF blocking substance is a soluble cytokine receptor.
- 25 12. Use according to claim 11, wherein soluble cytokine receptor is etanercept.
13. Use according to claim 11, wherein soluble cytokine receptor is lenercept.
14. Use according to claim 4, wherein said specific TNF blocking substance is a TNF receptor antagonist.
- 30 15. Use according to claim 4, wherein said specific TNF blocking substance is an antisense oligonucleotide.
16. Use according to any one of the claims 1-3, wherein said TNF inhibitor is a non-specific TNF blocking substance.
- 35 17. Use according to claim 16, wherein said non-specific TNF blocking substance is an MMP inhibitor selected from the group consisting of tetra-

cyclines, Prinomastat, Batimastat, Marimastat, BB-3644, KB-R7785, TIMP-1, TIMP-2, adTIMP-1 and adTIMP-2.

18. Use according to claim 16, wherein said non-specific TNF blocking substance is a quinolone selected from the group consisting of Norfloxacin, Levofloxacin, Enoxacin, Sparfloxacin, Temafloxacin, Moxifloxacin, Gatifloxacin, Gemifloxacin, Grepafloxacin, Trovafloxacin, Ofloxacin, Ciprofloxacin, Pefloxacin, Lomefloxacin and Temafloxacin.

19. Use according to claim 16, wherein said non-specific TNF blocking substance is a thalidomide derivate selected from the group consisting of CC-1088, CDC-501, CDC-801, and Linomide.

20. Use according to claim 16, wherein said non-specific TNF blocking substance is selected from the group consisting of a lazarooids, nonglucocorticoid 21-aminosteroids, prostaglandins, cyclosporin, pentoxifyllin derivatives, hydroxamic acid derivatives, naphthopyrans, phosphodiesterase I, II, III, IV, and V-inhibitors, elancortin agonists, lactoferrin, peptides derived from lactoferrin, CT3, ITF-2357, PD-168787, CLX-1100, M-PGA, NCS-700, PMS-601, RDP-58, TNF-484A, PCM-4, CBP-1011, SR-31747, AGT-1, Solimastat, CH-3697, NR58-3.14.3, RIP-3, Sch-23863 and SH-636.

21. A method for treatment of low back pain wherein a therapeutically effective amount of a TNF inhibitor is administered to a patient.

22. A method for diagnosis of low back pain wherein a diagnostically effective amount of a TNF inhibitor is administered to a patient, and an improvement of the patient's condition is an indication of that the patient is afflicted with low back pain.

23. A method according to claim 21 or 22 wherein said low back pain is due to local irritation of annulus related nerve fibers by disc derived substances.

24. A method according to claim 21 or 22, wherein said TNF inhibitor is a specific TNF blocking substance.

25. A method according to claim 21 or 22, wherein said TNF inhibitor is an antibody.

26. A method according to claim 21 or 22, wherein said TNF inhibitor is a monoclonal antibody.

27. A method according to claim 21 or 22, wherein said TNF inhibitor is infliximab.

28. A method according to claim 21 or 22, wherein said TNF inhibitor is CDP-571.

29. A method according to claim 21 or 22, wherein said TNF inhibitor is CDP-870.

5 30. A method according to claim 21 or 22, wherein said TNF inhibitor is D2E7.

31. A method according to claim 21 or 22, wherein said TNF inhibitor is a soluble cytokine receptor.

10 32. A method according to claim 21 or 22, wherein said TNF inhibitor is etanercept.

33. A method according to claim 21 or 22, wherein said TNF inhibitor is lenercept.

34. A method according to claim 21 or 22, wherein said TNF inhibitor is a TNF receptor antagonist.

15 35. A method according to claim 21 or 22, wherein said TNF inhibitor is an antisense oligonucleotide.

36. A method according to claim 21 or 22, wherein said TNF inhibitor is a non-specific TNF blocking substance.

20 37. A method according to claim 21 or 22, wherein said TNF inhibitor is an MMP inhibitor selected from the group consisting of tetracyclines, Prinomastat, Batimastat, Marimastat, BB-3644, KB-R7785, TIMP-1, TIMP-2, adTIMP-1 and adTIMP-2.

25 38. A method according to claim 21 or 22, wherein said TNF inhibitor is a quinolone selected from the group consisting of Norfloxacin, Levofloxacin, Enoxacin, Sparfloxacin, Temafloxacin, Moxifloxacin, Gatifloxacin, Gemifloxacin, Grepafloxacin, Trovafloxacin, Ofloxacin, Ciprofloxacin, Pefloxacin, Lomefloxacin and Temafloxacin.

30 39. A method according to claim 21 or 22, wherein said TNF inhibitor is a thalidomide derivate selected from the group consisting of CC-1088, CDC-501, CDC-801, and Linomide.

35 40. A method according to claim 21 or 22, wherein said TNF inhibitor is selected from the group consisting of a lazarooids, nonglucocorticoid 21-aminosteroids, prostaglandins, cyclosporin, pentoxifyllin derivatives, hydroxamic acid derivatives, naphthopyrans, phosphodiesterase I, II, III, IV, and V-inhibitors, elancortin agonists, lactoferrin, peptides derived from lactoferrin CT3, ITF-2357, PD-168787, CLX-1100, M-PGA, NCS-700, PMS-601, RDP-

58, TNF-484A, PCM-4, CBP-1011, SR-31747, AGT-1, Solimastat, CH-3697, NR58-3.14.3, RIP-3, Sch-23863 and SH-636.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/00671

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/00, A61K 39/395, A61P 29/00, A61P 25/00  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, BIOSIS, MEDLINE, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0018409 A1 (A+ SCIENCE INVEST AB), 6 April 2000 (06.04.00), page 1, line 10 - line 12; page 2, line 33 - page 3, line 2; page 4, line 18 - line 19, page 11, line 32 - page 12, line 11 --	1-40
X	US 6015557 A (TOBINICK ET AL), 18 January 2000 (18.01.00), column 4, line 13 - line 16; column 5, line 26 - line 55 --	1-40
X	US 6177077 B1 (TOBINICK), 23 January 2001 (23.01.01), column 2, line 11 - line 24; column 4, line 7 - line 12 --	1-40

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search  24 June 2002	Date of mailing of the international search report  09 -07- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer  ANNA BJÖRKLUND/BS Telephone No. + 46 8 782 25 00



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/00671

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0162272 A2 (IMMUNEX CORPORATION), 30 August 2001 (30.08.01), page 14, line 7 - line 9, claims --	1-40
P,X	US 2001027175 A1 (OLMARKER ET AL), 4 October 2001 (04.10.01) --	1-40
P,X	US 2001016195 A1 (TOBINICK), 23 August 2001 (23.08.01), abstract, page 4, paragraph 54-60; page 5, paragraphs 64 and 65 --	1-40
P,X	US 2001026801 A1 (TOBINICK), 4 October 2001 (04.10.01), abstract, page 4, paragraph 53-59 --	1-40
A	BIOSIS, PREV200000150653, Volume 25, No. 4, Luoma Katariina et al: "Low back pain in relation to lumbar disc degerertion", pages 487-492, Spine, Feb. 15, 2000 -- -----	1-40

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE02/00671

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 21-40  
because they relate to subject matter not required to be searched by this Authority, namely:  
see next sheet\*
2. ☒ Claims Nos.: 1-40, partially  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
see next sheet\*\*
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Since it is previously known to use TNF-inhibitors in pharmaceutical compositions for the treatment of pain in the back caused by an injured intervertebral disc, the inventions according to claims 4-20 and 24-40 lack a technical relationship involving a common special technical feature. Consequently, the inventions do not satisfy the requirements of unity and involves an unknown number of inventions.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE02/00671

\*

Claims 21-40 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

\*\*

The present application relates to a large number of possible compounds, which are defined by reference to a desirable characteristic or property, namely the ability to inhibit tumor necrosis factor (TNF). The claims cover all compounds having this characteristic or property, while the application lacks direct support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for all enumerated compounds but one, namely the monoclonal antibody infliximab. Expressions such as "TNF receptor antagonist", "non-specific TNF blocking substance", "phosphodiesterase I inhibitor", "elancortin agonists" etc. are also unclear. In the present case, the claims relate to so many possibilities and are so unclear that a meaningful search over the whole of the claimed scope is impossible. Therefore, the search has been limited and focused on compounds described as being TNF inhibitors, rather than on specific substances.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/00671

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	0018409	A1	06/04/00	AU	6491899 A	17/04/00
				BR	9913926 A	19/06/01
				CN	1326351 T	12/12/01
				CZ	20010983 A	13/02/02
				EP	1115405 A	18/07/01
				SE	9803276 D	00/00/00
				SE	9803710 A	26/03/00
				US	2001027175 A	04/10/01
				US	2001027199 A	04/10/01
				US	2001055594 A	27/12/01
US	6015557	A	18/01/00	AU	2616100 A	14/09/00
				EP	1161260 A	12/12/01
				US	6177077 B	23/01/01
				US	2001004456 A	21/06/01
				US	2001016195 A	23/08/01
				US	2001026801 A	04/10/01
				WO	0050079 A	31/08/00
				US	6379666 B	30/04/02
US	6177077	B1	23/01/01	AU	2604301 A	16/07/01
				US	6379666 B	30/04/02
				US	2001004456 A	21/06/01
				US	2001016195 A	23/08/01
				US	2001026801 A	04/10/01
				WO	0149321 A	12/07/01
				AU	2616100 A	14/09/00
				EP	1161260 A	12/12/01
				US	6015557 A	18/01/00
				WO	0050079 A	31/08/00
WO	0162272	A2	30/08/01	AU	4363200 A	02/11/00
				AU	4533601 A	03/09/01
				EP	1171148 A	16/01/02
				US	2001021380 A	13/09/01
				WO	0062790 A	26/10/00
US	2001027175	A1	04/10/01	AU	6491899 A	17/04/00
				BR	9913926 A	19/06/01
				CN	1326351 T	12/12/01
				CZ	20010983 A	13/02/02
				EP	1115405 A	18/07/01
				SE	9803276 D	00/00/00
				SE	9803710 A	26/03/00
				US	2001027199 A	04/10/01
				US	2001055594 A	27/12/01
				WO	0018409 A	06/04/00
				AU	4156000 A	21/11/00
				BR	0010364 A	13/02/02
				EP	1198922 A	24/04/02
				SE	514105 C	08/01/01
				SE	9901671 A	08/11/00
				WO	0069113 A	16/11/00

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/00671

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
US	2001016195	A1	23/08/01	US	2001026801 A	04/10/01
				US	2001004456 A	21/06/01
				AU	2604301 A	16/07/01
				US	6177077 B	23/01/01
				US	6379666 B	30/04/02
				WO	0149321 A	12/07/01
				AU	2616100 A	14/09/00
				EP	1161260 A	12/12/01
				US	6015557 A	18/01/00
				WO	0050079 A	31/08/00
-----						
US	2001026801	A1	04/10/01	US	2001016195 A	23/08/01
				US	2001004456 A	21/06/01
				AU	2604301 A	16/07/01
				US	6177077 B	23/01/01
				US	6379666 B	30/04/02
				WO	0149321 A	12/07/01
				AU	2616100 A	14/09/00
				EP	1161260 A	12/12/01
				US	6015557 A	18/01/00
				WO	0050079 A	31/08/00
-----						